IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HERON THERAPEUTICS, INC., Plaintiff, v. FRESENIUS KABI USA, LLC, Defendant.	C.A. No. 22-985-WCB **UNREDACTED PUBLIC VERSION**

DEFENDANT FRESENIUS KABI USA, LLC'S POST-TRIAL ANSWERING BRIEF

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TABLE OF ABBREVIATIONS

ABBREVIATION	FULL DESCRIPTION	EXHIBIT NO.
'229 patent	U.S. Patent No. 9,561,229	JTX1
'794 patent	U.S. Patent No. 9,974,794	JTX7
Agarwal	Apoorva Agarwal et al., *Process Optimisation, Characterisation and Evaluation of Resveratrol-Phospholipid Complexes Using Box-Behnken Statistical Design*, 3 INT'L CURRENT PHARMACEUTICAL J. 301 (2014)	JTX167
ANDA	Abbreviated New Drug Application	
Asserted Claims	Claims 9, 10, and 21 of the '229 patent and claims 9 and 10 of the '794 patent	
CINV	chemotherapy induced nausea and vomiting	
CN845	Chinese Patent Application Publication No. CN102379845A, titled "Aprepitant microemulsion for injection and preparation method thereof," filed on November 3, 2011	JTX17
Coors	Esther A. Coors et al., *Polysorbate 80 in Medical Products and Nonimmunologic Anaphylactoid Reactions*, 95 ANNALS ALLERGY, ASTHMA & IMMUNOLOGY 593 (2005)	JTX126
Emend IV	Emend for Injection	
EP279	Bombardelli et al., EP0441279A1 (published Aug. 14, 1991)	JTX74
FDA	United States Food and Drug Administration	
Fell	Gillian L. Fell et al., *Intravenous Lipid Emulsions in Parenteral Nutrition*, 6 ADVANCES NUTRITION 600 (2015)	JTX76
Fresenius's ANDA Product	The drug product that is the subject of Abbreviated New Drug Application No. 214639	
Fresenius Kabi	Fresenius Kabi USA, LLC	
Hargreaves	Richard Hargreaves et al., *Development of Aprepitant, the First Neurokinin-1 Receptor Antagonist for the Prevention of Chemotherapy-Induced Nausea and Vomiting*, 1222 ANNALS N.Y. ACAD. SCI. 40 (2011)	JTX82
Heron	Heron Therapeutics, Inc.	
Hingorani	U.S. Patent Appl. Pub. No. 2013/0317016 A1F	JTX21
HLB	Hydrophilic-Lipophilic Balance	
IV	intravenous	
Jumaa	Muhannad Jumaa & Bernd W. Müller, *Lipid Emulsions as a Novel System to Reduce the*	JTX88

ABBREVIATION	FULL DESCRIPTION	EXHIBIT NO.
	Hemolytic Activity of Lytic Agents: Mechanism of the Protective Effect, 9 EUR. J. PHARMACEUTICAL SCIS. 285 (2000)	
Kamat	Madhav Kamat & Patrick P. DeLuca, *Formulation Development of Small and Large Volume Injections*, in PHARMACEUTICAL DOSAGE FORMS: PARENTERAL MEDICATIONS (Sandeep Nema & John D. Ludwig eds., 3d ed., 2010)	JTX92
Karavas	International Patent Appl. Pub. No. WO 2014/005606 A1	JTX90
Khan	Barket Ali Khan et al., *Basics of Pharmaceutical Emulsions: A Review*, 5 AFRICAN J. PHARMACY & PHARMACOLOGY 2715 (2011)	JTX91
Liu	Jie Liu et al., *Progress in Research of Injectable Microemulsion*, 42 CHINESE J. PHARMACEUTICALS 300 (2011)	JTX93
NDA	New Drug Application	
NK-1	Neurokinin-1	
Patents-in-Suit	The '229 patent and the '794 patent	
PFAT5	Percentage of fat globules greater than 5 microns	
POSA	person of ordinary skill in the art	
[page]:[line]	format for trial transcript citations	
Strickley	Robert G. Strickley, *Solubilizing Excipients in Oral and Injectable Formulations*, 21 PHARMACEUTICAL RES. 201 (2004)	JTX105
USP	United States Pharmacopeia	
USP 1	United States Pharmacopeia, Chapter 1 (2014)	JTX107
USP 729	United States Pharmacopeia, Chapter 729 (2014)	JTX120
USPTO	United States Patent and Trademark Office	
Wan	U.S. Patent Appl. Pub. No. 2011/0038925 A1	JTX112
Washington	C. Washington, *Stability of Lipid Emulsions for Drug Delivery*, 20 ADVANCED DRUG DELIVERY REVS. 131 (1996)	JTX113
Yue	Peng-Fei Yue et al., *Process Optimization, Characterization and Evaluation In Vivo of*	JTX114

ABBREVIATION	FULL DESCRIPTION	EXHIBIT NO.
	Oxymatrine-Phospholipid Complex, 387 INT'L J. PHARMACEUTICS 139 (2010)	
Zhou or the Zhou article	Wei Zhou et al., *Preparation of Aprepitant Emulsion for Intravenous Injection*, 43 CHINESE J. PHARMS. 1003 (2012)	JTX115

I. Introduction

Faced with CN845, which indisputably taught aprepitant emulsion formulations by the priority date, Heron resorts to criticizing that reference for failing to disclose *each* of the claimed excipient amounts and associated physical stability data within one embodiment. But this is not an anticipation case. Based on the full scope and content of the prior art (CN845, Zhou, Washington, Liu) and a POSA's knowledge, the Asserted Claims are obvious.

CN845 showed various working emulsions using aprepitant, and Zhou gave promising stability results, so a POSA in view of Washington, Liu, and/or the knowledge of a POSA would have been motivated to optimize for USP with a reasonable expectation of success. While Heron addressed Washington's example of a "Class II" drug, it failed to mention that aprepitant is a "Class III" drug and that Washington taught increasing "surface area" for Class III drugs to reside on the "interface." Heron contradicts itself when criticizing Zhou (sometimes saying it discloses stability, while other times it does not), and ignores how a POSA would next seek to optimize for USP. In fact, Heron completely disregards USP in its obviousness analysis.

Heron asserts secondary considerations largely in conclusory fashion, and does not connect the alleged secondary considerations to the Asserted Claims to support the requisite nexus. In any event, none of the secondary considerations supports non-obviousness, especially in view of CN845, which already disclosed aprepitant emulsions to be optimized.

For infringement, Heron all but admits (and certainly does not dispute) inherency when it argues that Fresenius Kabi infringes the "physically stable" limitation (including the microscopy requirement) based on its formulation being the same as Cinvanti's. For written description, even though the patent specification distinguishes examples with a "pH of less than 8.0," Heron never explains how the patents showed the named inventors possessed the entire pH range of 7.5 to 9.0 (particularly the subset 7.5 to 8.0); nor does the evidence support such possession.

II. The Asserted Claims Would Have Been Obvious To A POSA

CN845 already taught aprepitant emulsions using oil, emulsifier, co-emulsifier, and a protective agent in enabled ranges, along with pH adjustment to 6.0-8.0. Heron failed to respond to the trial evidence that Washington, Liu, and a POSA's knowledge all showed that increasing emulsifier levels increased physical stability, and that a POSA would have used more than 10% emulsifier as part of routine optimization (including up to 30%, as disclosed in the art). Heron does not address the fact that Zhou tested for K_e, demonstrating promising stability and supporting further work to optimize the formulation for USP stability with a reasonable expectation of success.

A. Fresenius Kabi Showed Obviousness Under Either POSA Definition

Both formulation experts agreed that their opinions did not change based on the POSA definition. 130:15-17 (Rabinow); 1214:6-14 (Little). Heron asserts that Dr. Rabinow's POSA definition used "impermissible hindsight" because it identified "experience with emulsions," whereas Dr. Little's definition referenced experience "with parenteral drug products." D.I. 180 at 17-18. Identifying a POSA as someone who could follow CN845's teachings is not hindsight. "[P]rior art solutions" to problems encountered in the art can be considered when defining a POSA. *See, e.g.*, *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (citations omitted). Dr. Rabinow's definition was based on the prior art, because CN845 and other prior art aprepitant formulation references used emulsions. CN845 (JTX71); Zhou (JTX115); Karavas (JTX90); Hingorani (JTX21). In fact, Dr. Little confirmed that his POSA definition would include "experience with emulsion formulations." 1214:6-14. In any event, Heron never addresses Dr. Rabinow's opinions based on the assumption that Dr. Little's POSA definition applied.

B. Heron Fails To Diminish The Significance of CN845

Heron asserts that CN845 disclosed "broad ranges" of excipients, D.I. 180 at 23, but ignores that Dr. Little agreed that the CN845 examples "made emulsions" across the ranges and

excipients disclosed therein, 1373:6-1375:15. Once confronted with ranges that included the claimed invention, it was up to Heron to show criticality. Heron did not even try. To the contrary, Example 3 in the Patents-in-Suit showed that the claim limitations were not critical to physical stability, because none of these concentrations matched the concentrations from asserted claims 8 and 9 of the Patents-in-Suit, and claim 21 of the '229 patent: 0.587 wt/wt% aprepitant, 11.7 wt/wt% lecithin, 7.83 wt/wt% oil, and 20.4% sucrose. DDX4-1; JTX1.15, .18. As for claim 10 of the Patents-in-Suit, which recites 2-6 wt/wt% ethanol, both Example 1 (7.78 wt/wt%) and Example 6 (6.51 wt/wt%) show that ethanol amount is also not critical, as both were still "physically stable" formulations. JTX1.14, .16, .18. In fact, claims Heron previously asserted included broader ranges that were still "physically stable" formulations. *See* JTX 1 (claim 1); JTX7 (claim 1).

A POSA would have found CN845 reliable, contrary to Heron's suggestion that typographical errors, the term "microemulsion," and alleged "gaps" in the formulation instructions "raise questions" that would have "left a POSA guessing," D.I. 180 at 28 n.16. Both parties' formulation experts agreed that a POSA reading CN845 would have understood it was teaching conventional emulsions despite using the term microemulsion, and that these terms were regularly used interchangeably in the art. 1375:16-1376:7, 1421:24-1424:2 (Little); 160:23-163:19, 189:22-191:8 (Rabinow). Dr. Little also confirmed that despite "raising questions," a POSA would not have disregarded CN845 and would have seen they made emulsions. 1234:13-21, 1373:6-1374:15 (Little). Dr. Little even agreed that Example 4 in the Patents-in-Suit was based on a POSA's understanding of how a POSA would have known to implement CN845. 1401:21-1402:1.

C. CN845 Already Solved The IV Aprepitant Problem, So It Cannot Be Hindsight To Show a POSA Would Have Used and Optimized CN845

Heron argues "the problem facing a POSA was to develop a new IV NK-1 receptor antagonist" generally (rather than an aprepitant emulsion). D.I. 180 at 18. However, other NK-1

inhibitors undergoing clinical trials were already formulated for IV administration, and the prior art did not disclose how to improve them; whereas, the reasons to develop an IV formulation of aprepitant were well documented. CN845 itself expressly identified a motivation to create an IV aprepitant product, explaining that "[a]prepitant injectable dosage forms are of great significance for the clinical treatment." JTX71.12 at [0006]. CN845 pointed to aprepitant's already-established efficacy as an NK-1 receptor antagonist, its approved availability as an oral formulation, and its benefits over fosaprepitant. *Id.*; *see also* JTX71.11 at [0002]. Hingorani also expressly reported "there is a need for a stable liquid formulation of aprepitant for parenteral delivery." JTX21.2 at [0009]. Similarly, Karavas reported the "main object" of its efforts was to create an "injectable formulation containing a neurokinin 1 receptor antagonist, and in particular Aprepitant or Fosaprepitant." JTX90.3 at ll.25-29.

Heron next argues there were multiple NK-1 receptor antagonists that had "succeeded" because they completed phase III clinical trials. D.I. 180 at 18. But Heron ignores that none of these were FDA-approved, as phase III trials are only one step. 978:19-22 (Hale). As Dr. Hale admitted, a POSA would need to consider "several lenses," including "scientific," "business strategy," "IP advantages or disadvantages" to evaluate whether to pursue reformulation of an unapproved drug. 979:22-980:14. While arguing that aprepitant's aqueous insolubility "precluded" IV formulation, D.I. 180 at 19, Heron relies on outdated references that were "not about formulation techniques," 966:10-972:8, 988:6-21, 996:20-25 (Hale); PTX-3. Moreover, Heron relies on the lack of awareness of medicinal chemists from the 1990s, suggesting that would discourage a POSA as of the 2014 priority date. Heron's reliance on Dr. Hale (a medicinal chemist), who does not meet the qualifications for a POSA under either party's definition, must fail, D.I. 150 at 6; 968:19-21, 969:21-23, 971:6-16 (Hale). To this end, Dr. Hale credited Heron as

having "cracked this problem" of formulating aprepitant and gave it "kudos," (955:10-956:5), even though Dr. Hale never read CN845 that had already solved the problem, (997:13-24).

Heron asserts that Dr. Rabinow should have considered other formulation approaches, and that he used hindsight to pick the emulsion references. D.I. 180 at 20-21. To support this conclusion, Heron relies exclusively on general outlines like Strickley and Kamat—both published before 2014—which do not rule out emulsions, and are not directed to formulating NK-1 inhibitors, much less aprepitant. By the 2014 priority date, aprepitant emulsions were already known and used. *See, e.g.*, CN845 (JTX71); Zhou (JTX115); Karavas (JTX90); Hingorani (JTX21). As Dr. Rabinow succinctly stated, "if CN is already there, and they say this is the way to go, why wouldn't somebody follow it?" 268:19-269:9. It is not hindsight to follow what the prior art taught and directed the POSA to pursue. Heron offered no evidence about other NK-1 formulations that could have been plausibly pursued, but even if it had, "obviousness 'does not require that the motivation be the best option, only that it be a suitable option from which the prior art did not teach away.'" *Bayer Pharma AG v. Watson Labs, Inc.*, 874 F.3d 1316, 1328 (Fed. Cir. 2017) (citing *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014)).

Moreover, Dr. Rabinow ***did*** consider other formulation approaches, explaining that even if a POSA assumed they had not already been tried, "it would have been easy to do those experiments and discard them." 268:19-269:9. Dr. Rabinow summarized the state of the art, 268:2-18, explained that nanosuspensions were already used for the oral aprepitant formulation, 120:25-121:17, and even specifically addressed the teachings of Strickley, Kamat, and his own article that confirm that emulsions could be used when appropriate, 270:11-274:9 (Rabinow (discussing JTX105.25-26)); 275:17-277:21 (Rabinow (discussing JTX92.33-34)). CN845 already showed emulsions were in fact appropriate for aprepitant, making that an obvious approach.

D. Heron Did Not Address Motivation To Combine References

Ironically, while accusing Fresenius Kabi of using hindsight, Heron analyzed "motivation" to achieve individual claim limitations—separately for limitations as to 14% egg lecithin, sodium oleate, and "other claimed ingredients and in the claimed amounts"—instead of the motivation to combine prior art references. D.I. 180 at 28-44. A POSA would have been motivated to implement the aprepitant emulsion formulations disclosed in CN845 and optimize for USP for several reasons.

1. Heron Ignored Washington's Teachings For Class III Drugs

According to Heron, Washington "contradicts" Dr. Rabinow's opinion to increase egg lecithin, based on the S-emopamil example that used 1.2% egg yolk lecithin. D.I. 180 at 36. Dr. Rabinow, however, explained that S-emopamil was a "Class II" drug—one that Washington labeled "predominantly oil-soluble" and for which conventional emulsifier amounts were sufficient. 364:12-16, 448:2-449:11; JTX113.9. In contrast, aprepitant was a known "Class III" drug, one that is "poorly soluble in both water and oil," so naturally that was the focus of Dr. Rabinow's testimony. JTX113.9. Heron never mentions Washington's discussion of Class III drugs, and therefore completely sidesteps the core disclosure that would have explained to a POSA why CN845 worked: Class III drugs can be "loaded into an emulsion by adsorbing to the droplet interface." *Id*. Washington would have encouraged a POSA to increase emulsifier levels to increase stability. Washington even made the connection between available interface and the need for a "large surface area available for loading." *Id*.; *see also* 173:19-174:15 (Rabinow).

2. Heron Ignored USP

USP requirements provided the motivation to combine references to optimize CN845 and Zhou. Heron's choice to avoid the USP undermines several of its arguments. First, Heron states there would be no reason to further optimize aprepitant formulations, but both named inventors and Dr. Little agreed with Dr. Rabinow that a POSA would have pursued USP stability. 468:10-

469:3 (Han); 521:16-522:12 (Ottoboni); 1267:1-1268:7 (Little) ("a standard that's put forth that you would have to meet for stability if you were making a commercial product"). Second, Heron claims that Zhou optimized for stability, asserting that "Zhou already teaches a POSA a stability-optimized aprepitant emulsion," D.I. 180 at 38, and that Zhou used "significantly less egg lecithin (2.5%) than the Asserted Claims (14%)," *id.* at 30, 45. But those arguments completely ignore Dr. Rabinow's testimony that Zhou optimized for K_e not USP, and the POSA's obvious step in view of CN845 and Zhou would have been to optimize for USP. 226:15-227:3. Third, to avoid having to admit that a POSA would have next optimized for USP stability and using increased emulsifier as needed, Heron uses that phrase "stability-oriented" to imply Zhou already tested for USP stability. Heron knows that Zhou optimized for K_e not USP. *See* D.I. 180 at 25 n.11. Heron cites *Janssen* and *Leo* for the general proposition that a reason to modify shows obviousness. D.I. 180 at 35-36 (citing *Janssen Pharms., Inc. v. Tolmar, Inc.*, No. 21-1784, 2024 WL 834762, at *20 (D. Del. Feb. 26, 2024); *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013)). But Heron never addresses or distinguishes Dr. Rabinow's testimony that a POSA would have been motivated to modify CN845 and Zhou to achieve USP stability, and that Zhou's results would have given a POSA a reasonable expectation of success to achieve USP stability. 238:3-239:5.

3. Heron's Microemulsion/Emulsion Distinction To Avoid Liu Ignores The State of the Art

A POSA looking to optimize the aprepitant emulsion formulations of CN845 and Zhou would have been motivated to increase the amount of emulsifier. 250:21-251:25 (Rabinow). The prior art provided guidance about emulsifier levels; Liu specifically showed a POSA that up to 30% of emulsifier was used in other emulsion formulations and would be suitable for optimizing an aprepitant emulsion formulation. *Id.*, 226:15-227:3, 223:1-8; JTX93.10-.11.

Heron seeks to discredit Liu based on an artificial nomenclature issue, *see* D.I. 180 at 31;

however, Dr. Little already conceded that a POSA would have understood that "microemulsions" and "emulsions" are overlapping terms: a microemulsion is "a category of emulsion," 1422:1-4 (Little). Dr. Rabinow similarly testified that Liu described the disclosed microemulsions as "a subset of emulsions." 342:19-24. Fresenius Kabi also showed that other references used the terms interchangeably. *Id*. (citing JTX91.3; JTX110.3 at [0009]); *see also* 445:21-446:9 (Rabinow) (testifying a POSA would have "recognize[d] that there wasn't a clear distinction between the two"); 446:10-447:2 (Rabinow) (discussing "continuum").

The testimony further supports that reference to "microemulsion" would not reduce the relevance of the prior art to a POSA. For example, Dr. Rabinow and Dr. Little agreed that CN845 used "microemulsion" in the title and described a classical definition of the term, although it developed and disclosed emulsions. 161:3-162:24 (Rabinow); 1240:16-1241:16 (Little). Dr. Rabinow also explained that "[i]f you're asking me in the context of selecting a maximum concentration of surfactant, which has been defined -- which has been found for microemulsions, is that applicable for emulsions, I would say yes, of course it is." 339:18-340:3.

4. Heron Ignores What A POSA Would Have Understood About Complexation

Heron argues that "CN845 does not mention complexing, let alone provide any data showing it occurred." D.I. 180 at 34. Dr. Little agreed, however, that CN845's process reflected "one way of making a complex." 1386:23-1387:1. Heron's experts did not rebut Dr. Rabinow's explanation that a POSA would have understood CN845's process to "go to the trouble" of bringing together aprepitant and egg yolk lecithin disclosed complexation. *See* 154:4-156:15.

Heron then asserts that even if CN845 did teach complexation (which it does), there would be no reason to increase emulsifier concentration to increase complexation. D.I. 180 at 35-36. But that ignores the crux of Dr. Rabinow's point (as supported by the prior art): the emulsifier formed

an emulsion, the emulsifier added surface area "real estate," and the emulsifier also helped "solubilizing" the drug as Zhou reported. 156:16-157:14, 217:14-218:12, 356:15-357:14 (Rabinow). Dr. Little argued that Dr. Rabinow's "life preserver" analogy was "a geometric impossibility," because the emulsifier mass would be greater than oil. D.I. 180 at 37 n.20; 1231:4-12. It lacks credibility to assert "impossibility", when CN845 already used more emulsifier than oil (Example 7), as did Examples 1, 2, 3, 4 and 6 in the Patents-in-Suit. JTX71.17; JTX7.14-16.

Heron criticizes the Agarwal, Yue, and EP279 references, which Dr. Rabinow discussed disclosed examples of complexation. D.I. 180 at 35. Dr. Rabinow used these to show that a POSA was very familiar with complexation, specifically using egg yolk phospholipid—not only the preferred emulsifier in CN845 but also the preferred emulsifier a POSA would have considered. 178:2-181:19. Heron's experts never rebutted Dr. Rabinow's opinions that a POSA would have preferred egg yolk phospholipid, or that a POSA would have been aware of complexation.

5. Obviousness Does Not Depend On Combining Eleven References

Heron alleges hindsight based on the number of references that Dr. Rabinow discussed. D.I. 180 at 21-23. But not all references were used in a combination. Some were background, and some showed a POSA's knowledge. *Pernix Ireland Pain v. Alvogen Malta Ops.*, 323 F. Supp. 3d 566, 597 (D. Del. 2018) (discussing different types of references). The references all showed what a POSA would have understood in view of CN845. That is not hindsight; that is merely following the art as a POSA would have done. *See, e.g.*, *Bayer*, 874 F.3d at 1323 (overturning district court's finding of no motivation because defendant had presented "a significant number of references" (nine) pointing toward the same motivation).

Neither of the district court cases cited by Heron ever addresses whether a "volume" of references may point toward hindsight. *Endo* was a chemical compound case where the dispute was primarily whether the "lead compound" had been selected properly, not whether the number

of references in the combination had any impact on obviousness. *See Endo Pharm. Inc. v. Mylan Pharm. Inc.*, No. 11-CV-00717 (RMB/KW), 2014 WL 334178, at *14 (D. Del. Jan. 28, 2014). *Cephalon* raised no question as to the number of references either; instead, it focused on whether the patent challenger showed the prior art was able to "collectively, although not explicitly, guide an artisan of ordinary skill toward a particular solution." *Cephalon Inc. v. Mylan Pharms., Inc.*, 962 F. Supp. 2d 688, 717 (D. Del. 2013) (internal citations and quotations omitted).

In this case, the prior art itself led the way. Nevertheless, one of Heron's accusations of hindsight suggests Dr. Rabinow testified first about what the Asserted Claims said, and then showed where those limitations were found in the prior art. D.I. 180 at 21-22. But the testimony to which Heron refers involves Dr. Rabinow's *Graham* comparison of the Asserted Claims to the prior art, well ***after*** he had thoroughly addressed what the prior art would have taught a POSA, without referencing the claims. 225:25-227:3. Therefore, this case is nothing like *In re Kotzab*, where the Examiner assumed the prior art applied to the claims, without supporting prior art disclosures. 217 F.3d 1365, 1370-71 (Fed. Cir. 2000).

E. The POSA Applying The Prior Art Would Have Arrived At The Claimed Invention With A Reasonable Expectation of Success

As Dr. Rabinow testified at trial, CN845 taught a POSA "exactly how to make a successful injectable emulsion of aprepitant. "It told you exactly what to use and how much to use. And it also taught you how to combine them." 141:15-20. The remainder of the prior art references confirm how a POSA would have implemented CN845.

1. Heron Does Not Dispute Most Claim Limitations

Heron does not dispute the claim limitations for 0.7 wt/wt% aprepitant (all claims), the selection of soybean oil and egg yolk phospholipid (all claims), the 7.5-9.0 pH range (all claims), or the 2-6% ethanol (claim 10). The fact that Heron does not contest these limitations show that

the emulsion components were clearly present in the prior art. The invention as a whole would have been obvious, but the disputed components are addressed here to address the arguments.

2. Sodium Oleate, A Known pH Adjuster, Provided Stabilizing Benefits

Heron asserts that a POSA would not have selected sodium oleate as a pH adjuster, because it asserts a document did not expressly disclose "the use of sodium oleate to adjust pH." D.I. 180 at 39. It is not clear that the functional component of this claim limitation is required to be separately shown. Nonetheless, Dr. Rabinow testified that CN845 disclosed using a pH adjuster, and "a POSA would know that he could use sodium oleate" as a pH adjuster. 227:18-228:14. In fact, because sodium oleate and oleic acid are chemical conjugates of one another, they inherently adjust pH. 231:8-24 (Rabinow). Heron's experts never rebutted these facts. Zhou disclosed the benefits of adding oleic acid, and the basic pH 7.31. JTX115.7, .9-.11; *see also* 198:19-200:4 (Rabinow). Rather than adding oleic acid and then adding sodium hydroxide to get the desired basic pH, a POSA would have known to use sodium oleate, thereby both raising the pH and stabilizing the emulsion. 164:1-165:7, 200:5-202:15, 424:18-425:8 (Rabinow).

Sodium oleate's stabilizing effect would have provided another reason to use it. Wan confirmed the state of the art to add oleic acid/sodium oleate as a stabilizer in emulsions. JTX112.36, [0338]; *see also* 427:25-428:22 (Rabinow). The Fell review article reported the same (JTX76.4), which reflected prior art usage. 206:18-208:1 (Rabinow). Heron's experts never disputed that it described prior art usage.

Heron suggests that sodium hydroxide would have been more obvious for pH adjustment, but whether another option may be available or "obvious" does not take away from the obviousness of alternative available pH adjusters. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362-63 (Fed. Cir. 2007) (concluding selected salt form was an obvious option). Moreover, the evidence showed that even if sodium hydroxide were used, a POSA would have understood sodium oleate would

have still been in the formulation. That is because egg yolk lecithin already contains oleic acid which, when paired with sodium, becomes the sodium salt form of oleic acid, namely sodium oleate. 201:12-202:10, 377:21-378:4 (Rabinow). Dr. Little agreed this chemical balancing would inherently occur. 1416:13-17 (Little); 159:12-160:5 (Rabinow). Further, Heron never offered evidence of any criticality regarding this limitation. To the contrary, Heron tested sodium hydroxide formulations "instead of sodium oleate," and found those were also stable. 1416:24-1419:11 (Little); DTX191_168, _171. Indeed, the specification for the Patents-in-Suit lists sodium oleate as an option but that several others "may be used." JTX1.12, at 11:59-66.

Finally, regarding the safety of sodium oleate, Heron surprisingly asserts that "Dr. Rabinow has provided no explanation" why a POSA would select sodium oleate. D.I. 180 at 41. But Dr. Rabinow provided many in-depth explanations, which Heron's experts did not rebut. For example, Dr. Rabinow explained that Wan's report regarding hemolysis was due to the miglyol contained therein, because sodium oleate cannot intercalate as well with that triglyceride as compared to egg yolk lecithin. 383:10-385:2, 429:15-430:16 (Rabinow); JTX112.38 [358], Table 19. In other words, lecithin retains sodium oleate at the oil globule interface, so that it does not leak out of the formulation. *Id*. Dr. Rabinow then discussed Jumaa, which noted that while ordinarily sodium oleate is a "lytic agent," "a different behavior was observed in emulsions." JTX88.1, .3; 383:10-385:2 (Rabinow). The Abstract in Jumaa reports that "all emulsion formulations… showed a stable erythrocyte behavior." JTX88.1. Dr. Little did not mention Jumaa. Therefore, this case is distinguishable from *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1345-46 (Fed. Cir. 2013), where the Board erred by "ignoring teachings" that a process to modify cells could be toxic to and thus destroy those cells. Here, Dr. Rabinow provided several reasons why a POSA would not be concerned about using sodium oleate in an aprepitant

emulsion—especially using the egg yolk lecithin CN845 taught. 438:6-443:9, 454:20-456:11.

3. Heron's Attorney Argument Does Not Overcome CN845's Express Disclosure of Sucrose

Dr. Little admitted on cross examination that CN845 disclosed sucrose, 1368:2-8, 1375:7-9, and that he did not consider criticality compared to any amount of protectant, 1408:6-12. Nevertheless, Heron now argues that Dr. Rabinow should have identified an "FDA approved" formulation that used sucrose, and that he did not distinguish glycerin. D.I. 180 at 42-43 & n.21. There is no requirement that only FDA-approved formulations containing claimed excipients show obviousness, especially where (as here) CN845 both disclosed and tested sucrose formulations. JX71.13, .15. Heron also incorrectly reports that Dr. Rabinow chose, from CN845's list of protectants, "the only one that lined up," D.I. 180 at 43; in fact, Dr. Rabinow considered all of the listed protectants and opined that a POSA would have understood "you could select from" three as prime candidates: glycerin, sucrose, and glucose, 148:14-150:10. Dr. Rabinow also confirmed Heron did not identify any criticality for the selection between the disclosed protectants. 232:21-25. And Heron's own lab notebook once again confirms that there is no criticality between different protectants, for example testing glycerol and still seeing stable formulations. DTX191_53, _55. Indeed, the specification for the Patents-in-Suit lists sucrose as an option but that several other options for "a tonicity agent." JTX1.12, at 11:55-58.

4. A POSA Would Have Used Amounts Including 14% Egg Yolk Lecithin To Increase Stability And Meet USP Requirements

Heron cannot change the fact that slightly increasing the amount of stabilizer in an emulsion to increase stability is not an invention. Heron cites to another chemical compound case, which supports Fresenius Kabi's position. In *Eisai Co. Ltd. v. Dr. Reddy's Lab'ys. Ltd.*, 533 F.3d 1353, 1358 (Fed. Cir. 2008), the defendant's argument started with a lead compound and then dropped "the very feature" that gave it an "advantageous property." Here, the opposite is true:

Fresenius Kabi did not drop the "very feature" that enabled the CN845 emulsion—excess emulsifier—but showed that using more would help improve stability. As Dr. Rabinow summarized, "CN has shown that you need higher levels of emulsifier than are typically found in conventional emulsions" and "[t]he natural question would be have they gone high enough." 225:8-24. "There's nothing that said he couldn't go higher." 245:22-246:5 (Rabinow).

Heron faults Dr. Rabinow for focusing on increasing emulsifier levels, but not increasing other excipients like oil or ethanol. D.I. 180 at 42. But Khan expressly confirmed what a POSA would have known: "emulsifier concentration has a great impact on emulsion stability." JTX91.5; *see also* 169:1-13 (Rabinow). A POSA would have known from basic emulsion principles that increasing emulsifier levels increases surface area interface. 136:10-137:11 (Rabinow). Unlike the case law to which Heron cites, there was no "hodgepodge" analysis based on multiple features not in the prior art. D.I. 180 at 44 (citing *Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d 377, 421 (D. Del. 2021)). Rather, the prior art showed what to do here.

Heron asserts that Dr. Rabinow "did not specifically argue that a POSA would have reasonably expected that using 14% egg lecithin, sodium oleate as a pH modifier, or the entirety of the claimed combination would result in a stable aprepitant emulsion that was safe for intravenous use." D.I. 180 at 44. To the contrary, Dr. Rabinow explained that (i) higher than 10% egg yolk lecithin amounts were safe and that Liu confirmed "good safety," 222:16-25; (ii) "there's no problem with using sodium oleate in emulsions" that do not use miglyol, 383:10-385:2; and (iii) the rest of the formulation used components "administered to literally tens of millions of patients," 134:6-18, 146:14-25. He did so even though none of the Asserted Claims require any safety threshold and the Patents-in-Suit do not describe any safety testing.

The thing left for a POSA to do was test and optimize for USP requirements. As Dr. Little

understood, a POSA would have used "the smallest amount that you can" of an excipient as needed for a particular purpose. 1286:14-1288:13 (Little). No wonder then that CN845, Zhou, and Hingorani used lower emulsifier levels: they did not need more for their purposes. To optimize for USP, however, a POSA would have included increased emulsifier levels as appropriate. 218:16-219:23 (Rabinow). Importantly, the prior art did not discourage using more than 10% emulsifier. 245:18-246:5 (Rabinow).

Heron's criticisms about Liu are without merit. Heron asserts that the 5-30% surfactant range in Liu does not cover all of the Examples of CN845, D.I. 180 at 31, but CN845 did include the overlapping range of 0.5-10% emulsifier. As to the question of how high one could consider, the POSA would have engaged in routine experimentation using up to 30%; Dr. Little did not address Liu's reporting on the safety of using high emulsifier concentrations. Heron also asserts that Liu taught "water-in-oil" emulsions as opposed to "oil-in-water" emulsions. *Id*. at 34. Liu disclosed that phospholipids in general had "HLB" values that could be used for either type of emulsion. JTX.93.11-12 (showing the range 3-8 overlapped for either emulsion type). CN845 already disclosed oil-in-water emulsions using egg yolk lecithin, 295:1-14 (Rabinow), and a POSA would have known that egg yolk lecithin was used for oil-in-water emulsions. 1415:2-6 (Little).

Heron claims that Dr. Little discussed Khan and showed that "even 0.5% emulsifier can destabilize some emulsions," D.I. 180 at 36-37; however, Dr. Little never mentioned Khan. Khan described the general principle that, for an emulsion, "you can't have too little emulsifier" and "you can't have too much." 216:12-18, 250:3-251:14 (Rabinow). Heron also cites to Dr. Little for the premise that microemulsions must use different ingredients than emulsions, D.I. 180 at 32, but he never made that claim, only giving examples that they sometimes do. 1292:6-1293:7 (discussing JTX93.10-11).

5. Heron's Arguments Regarding Routine Optimization Are Deficient

CN845 already showed how to make an emulsion formulation, and Zhou already tested it for K_e stability; a POSA would have next optimized lecithin levels for USP stability with a reasonable expectation of success. 166:25-167:15, 194:6-12, 213:6-214:9 (Rabinow). As Dr. Little conceded, "the performance of a stability test is routine," and agreed that is so "even if it takes a long time." 1393:7-14. Dr. Little's admission confirms stability testing was "generally recognized as routine." *Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1348-49 (Fed. Cir. 2024).

When asked about routine optimization for lecithin levels, Dr. Little testified that Zhou already represented "an optimization that was done" and used "low single digit percents" of lecithin. 1282:20-1283:16. Dr. Little ignored the fact that Zhou optimized for K_e and not USP; whether Zhou ended up with lower numbers in the K_e context is not dispositive of a final result for USP optimization. Dr. Little admitted that "increasing the emulsifier in a system will reduce the globule size," with the only limitation that it "is not necessarily the case…that always happens." 1425:14-1426:13. Dr. Little's testimony supports routine optimization: testing ranges in order to identify effect on stability does not require proof of "always" increasing stability.

Heron asserts that Dr. Rabinow offered "no evidence showing why a POSA would have even tested the particular solution of 14 wt/wt % egg lecithin as optimization." D.I. 180 at 38-39. That position ignores Dr. Rabinow's expansive testimony where he explained that a POSA would test ranges higher than CN845, 225:8-24; a POSA would increase emulsifier levels beyond 10% in view of Washington, 228:21-229:8; and Liu expressly disclosed a range of 5-30% to support testing lecithin within that range, 222:16-223:14. Heron cites to *Unigene*. While not a range or routine optimization case, *Unigene* still supports Fresenius Kabi's position. There, the "primary inventive aspect" of the claims—the use of citric acid as an absorption enhancer—had an unclear function in the prior art, which amounted to "teaching away" for this function. *Unigene Lab'ys,*

Inc. v. Apotex, Inc., 655 F.3d 1352, 1363 (Fed. Cir. 2011). Here, CN845 expressly disclosed egg yolk lecithin as an emulsifier, and Heron did not even assert teaching away. The evidence about increasing emulsifier level to increase stability was not "vague" evidence, but rather "collectively although not explicitly" would have guided the POSA to the claimed solution. *Id*. at 1361. In response, Heron could have attempted to show criticality, but failed to do so. *See In re Geisler*, 116 F.3d 1465, 1469-70 (Fed. Cir. 1997) (affirming routine optimization obviousness).

Heron also relies on *Genetics Institute, LLC v. Novartis Vaccines & Diagnostics, Inc*. to characterize the number of formulations in CN845 as too large to render the Asserted Claims obvious. In *Genetics*, however, there were 68,000 variants at issue to try. 655 F.3d 1291, 1306 (Fed. Cir. 2011). Heron's rote recitation of the disclosure of excipients and amounts in CN845 does not compare to the vast disclosure in *Genetics*. Further, CN845 fully enabled its ranges, with Dr. Rabinow describing the "robust[]" disclosure, 230:19-231:7, and Heron even now referring to the "heterogeneity" of CN845's examples, D.I. 180 at 29. Dr. Little similarly worked through the types and ranges of excipients reflected in CN845 and confirmed they all made emulsions. 1373:6-16. Thus, the "prior art ranges that are not especially broad invite routine experimentation to discover optimum values." *Genetics*, 655 F.3d at 1306 (internal quotations omitted).

In *In re Patel*, the prior art did not give reasons to test a range above that expressly disclosed in one reference. 566 F. App'x 1005, 1009 (Fed. Cir. 2014). By contrast, CN845 taught excess emulsifier amounts, disclosing and testing ratios of 49:1 emulsifier:aprepitant; Washington taught that the drug will reside at the interface; and Liu disclosed ranges of 5-30% emulsifier. All would have motivated the POSA to use amounts higher than 10 w/w% of egg yolk lecithin as part of the routine optimization for USP compliance.

Heron cites *ModernaTx, Inc. v. Arbutus Biopharma Corporation*, 18 F.4th 1364 (Fed. Cir.

2021) to criticize Dr. Rabinow's analysis of the excipients and amounts to be optimized. *ModernaTx* discusses the situation where multiple and inter-connected result-effective variables are present in a claimed formulation. *See ModernaTx*, 18 F.4th at 1376. Heron presented no evidence regarding such interconnectivity. To the contrary, Dr. Rabinow provided unrebutted testimony that the lecithin level is the result-effective variable, 166:11-20, 167:20-168:23, 216:1-18, 219:18-23, 225:8-24, and that all of the other formulation components were used in ordinary amounts as compared to ordinary emulsions, 134:6-18. Dr. Rabinow provided extensive testimony on the process of routine optimization a POSA would have undertaken; therefore, *Intendis* is inapposite as it did not describe the "routine nature of optimizing a formulation." *Intendis GMBH v. Glenmark Pharms. Ltd.*, 117 F. Supp. 3d 549, 590-91 (D. Del. 2015), *aff'd*, *Intendis GMBH v. Glenmark Pharms. Inc., USA*, 822 F.3d 1355 (Fed. Cir. 2016).

F. At The Patent Office, Heron Did Not Distinguish The Actual Disclosed Examples From CN845 Or Zhou

Heron states that "Fresenius did not rely on a single document disclosing a formulation of aprepitant for intravenous use that the examiner had not already considered in allowing the claims." D.I. 180 at 11 (emphasis added). From this statement, Heron argues that Fresenius Kabi has a heightened burden of proof for invalidity. D.I. 180 at 12. Fresenius Kabi did rely on references that were not before the USPTO, including Washington and Liu. JTX113; JTX93. Regardless, the law is clear that "there is no heightened burden of proof when a reference was previously considered by the PTO." *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259-60 (Fed. Cir. 2012). Moreover, Heron did not actually test any CN845 example formulation or any CN845 or Zhou formulation using a pH above 7.0 (even though both disclosed pH above 7.0). So the USPTO never had an opportunity to consider an apples-to-apples, or closest prior art, comparison. "If the PTO did not have all material facts before it, its considered judgment may

lose significant force and the burden to persuade the finder of fact by clear and convincing evidence may, therefore, be easier to sustain." *Id*. at 1260 (internal quotations omitted).

During prosecution of the '229 patent, the Examiner rejected the pending claims as obvious over CN845 because it discloses the same excipients as those claimed "in ranges that touch, border on, overlap, or are close to the instantly claimed ranges," noting it was unclear whether the 3-5% difference in egg yolk lecithin from CN845 "will make any difference in the properties of the composition and is therefore routine optimization." JTX2.89, ¶¶ 41, 42. When the Examiner asked "if Applicant tried something like Ex. 4 of the spec. using Applicant's method as opposed to Zhou's," named inventor Ottoboni directed the Examiner to Example 5, which he claimed "is prepared using the method Applicant uses for examples according to their claimed invention." JTX2.108. But the evidence confirmed that Example 5 was an attempt to reproduce the Zhou article, which had a much lower amount of emulsifier and different pH. 544:11-546:12, 547:14-22 (Ottoboni); DTX 192_5; DTX190_3; 501:1-10, 503:1-13 (Han); 1419:12-1421:1 (Little). The Examiner suggested Dr. Ottoboni "provide a Declaration to explain any differences in the procedure of Ex. 4 vs. the process used in Zhou," and specifically referenced Example 1 of CN845. JTX2.108. Heron never actually followed any examples of CN845 let alone its Example 1. 490:17-20 (Han); 534:13-535:11, 540:6-541:8 (Ottoboni); 290:12-18 (Rabinow).

Heron alleges that criticality was demonstrated for a 20:1 ratio of egg yolk lecithin to aprepitant, and cites to the prosecution history. D.I. 180 at 12, 47 (citing JTX2.162-63). Dr. Little never attempted to show criticality for this ratio, nor do the Patents-in-Suit show criticality because Heron never tested different ratios while keeping constant other variables, including pH, aprepitant concentration, and emulsifier concentration. 288:19-293:2 (Rabinow). Heron also did not test Hingorani's aprepitant emulsions, which had 12:1 ratios of emulsifier to drug. 262:22-263:16

(Rabinow). Nor did Heron present testing evidence with ratios above 20:1, necessary to show criticality. Instead, the calculated ratio of 20:1 simply shows that more emulsifier made the formulation more stable. That was an obvious and expected conclusion, and does not show that the ratio of 20:1 is somehow critical. The Examiner did state that the prior art ratio of egg yolk lecithin to aprepitant was "far too low" when assessing claims that expressly recited a 20:1 ratio, JTX2.163; however, she overlooked the CN845's ratios, including the 49:1 ratio in Example 7, JTX71.17 (Example 7); 245:2-246:5 (Rabinow).

Heron never rebutted prima facie obviousness because it never actually compared its claimed invention to the closest prior art. *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc*., 97 F.4th 915, 933 (Fed. Cir. 2024) (citing *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 978 (Fed. Cir. 2014)). As in the recent *Otsuka* decision finding no deference was owed to the USPTO's review of a prior art article, Heron's "experiments followed processes that contained material differences from [the prior art]." *Otsuka Pharm. Co., Ltd. v. Lupin Ltd.*, No. 21-900-RGA, 2024 WL 3618123, at *18 (D. Del. July 31, 2024).

III. Heron's Secondary Considerations Arguments Do Not Overcome Obviousness

"Weak secondary considerations generally do not overcome a strong prima facie case of obviousness." *Genentech, Inc. v. Sandoz, Inc.*, 55 F.4th 1368, 1378 (Fed. Cir. 2022) (quoting *W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1371 (Fed. Cir. 2010)). None of Heron's arguments overcome Fresenius Kabi's strong showing of obviousness.

A. Claim Scope And Unclaimed Features Show A Lack Of Nexus

For its nexus argument, Heron relies on a presumption based on Cinvanti. "[O]bjective evidence of non-obviousness must be commensurate in scope with the claims which evidence is offered to support." *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (2008) (quoting *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983)). Here, the claimed formulation is not the reason for

any of the alleged secondary considerations, so Heron cannot rely on the mere presumption of nexus. *See Campbell Soup Co. v. Gamon Plus, Inc.*, 10 F.4th 1268, 1277 (Fed. Cir. 2021) (finding no presumed nexus where claims did not cover significant features of commercial embodiment).

Even if Heron were entitled to a presumption of nexus, that presumption is rebutted here. "Where the offered secondary considerations actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330 (Fed. Cir. 2017) (quoting *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)). Fresenius Kabi has shown that CN845 described polysorbate 80-free aprepitant emulsions for intravenous administration, D.I. 179 at 47 (citing 253:4-18, 255:3-8 (Rabinow); JTX71.14-17), and large-scale prospective studies had long ago shown that Emend and Emend IV already provided efficacy and low adverse events, *id*. at 41 (citing JTX73.5, .8; 604:11-605:20, 666:17-668:1 (Markman)).

B. There Is No Factual Or Legal Basis For Long-Felt, Unmet Need.

Heron recognizes that the standard to show long-felt, unmet need requires "an articulated identified problem and evidence of efforts to solve that problem" in the prior art. D.I. 180 at 49 (quoting *WBIP, LLC v. Kohler Co*., 829 F.3d 1317, 1334 (Fed. Cir. 2016)). But Heron never showed any such articulated problem or efforts to solve that problem. In *Genentech*, the patentee identified two benefits associated with the claimed invention, but failed to "establish any long-felt, unmet need" for the claimed invention. 55 F.4th at 1378. Heron's reliance on *WBIP* is misplaced because there, the prior art articulated houseboat carbon monoxide poisoning and included product liability suits, and the defendant had tried to solve that problem without success. 829 F.3d at 1334. Here, Dr. Roeland identified no articulated need associated with Emend IV side effects, nor did he identify efforts by others to unsuccessfully address any such problem. He never rebutted Dr. Markman's testimony that Heron failed to connect side effects with Emend IV and that physicians

knew how to manage any side effects from a regimen that included Emend IV. D.I. 179 at 41-45.

Nor did Dr. Roeland identify any efforts by others to solve the side effect problem that was somehow deemed insufficient. Instead, Heron recasts physicians' prior art side effect management as "workarounds" and then asserts that "the very need for such workarounds serves as 'evidence of efforts to solve that problem.'" D.I. 180 at 51 (quoting *WBIP*, 829 F.3d at 1334). Here again, *WBIP* supports Fresenius Kabi's position: the defendant in *WBIP* used workarounds unsuccessfully, because "Kohler's own documents show that even Kohler recognized the carbon monoxide poisoning problem persisted despite switching pipe materials." 829 F.3d at 1333.

Heron repeatedly cites the Coors article, but that article did not articulate any long-felt need about Emend IV. It did not even mention Emend IV or ISAEs; rather, it related to testing systemic "anaphylactoid reactions." JTX126.1; *see also* 671:11-25 (Markman). Coors therefore does not articulate a need to be solved or show that physicians were unable to address a need. In fact, to this day, Emend IV is still routinely administered. 1081:14-19 (Roeland).

If anything, Coors supports a motivation to avoid polysorbate 80 in formulations, as opposed to showing that any side effect problems associated with polysorbate 80 were medically unmanageable. CN845 already solved that formulation issue because it proposed formulations without polysorbate 80, and indeed recommended "preferably egg yolk phospholipid." JTX71.13. Heron's only distinction over CN845 is a difference in physical stability (between 10% and 14% emulsifier); Heron did not distinguish CN845 on any safety ground. "Where the differences between the prior art and the claimed invention are as minimal as they are here…it cannot be said that any long-felt need was unsolved." *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l. LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010). Heron's last-resort argument—that CN845 was not commercialized—does not matter. *See Azurity Pharm., Inc. v. Alkem Lab'ys Ltd.*, 655 F. Supp. 3d

270, 301 n.23 (D. Del. 2023) (rejecting patentee's argument "because no testimony was offered tying the lack of a commercially available [prior art product] to a lack of scientific know-how for making one"—as opposed to other considerations).

Heron relies on *Lundbeck* and *Eli Lilly*, but those cases are easily distinguishable. D.I. 180 at 49. In *Lundbeck*, the claims at issue addressed a need where medication was not used "due to [certain] adverse events," *Lundbeck v. Lupin Ltd.*, No. CV 18-88-LPS, 2021 WL 4944963, at *13 (¶¶ 73, 75), *59 (¶ 553) (D. Del. Sept. 30, 2021); here there was no such evidence. In *Eli Lilly*, the court found an unmet need because a prior product was removed from the market due to toxicity issues. *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1374 (Fed. Cir. 2006). Here, Emend IV was never removed from the market, had demonstrated acceptable levels of adverse events, and is still used today (1081:14-19 (Roeland)).

Heron appears to have abandoned supposed long-felt needs based on "rescue medicine" frequency and "bag shortage" issues.

C. There Was No Evidence At Trial Of Others Who Tried And Failed To Develop IV Formulations.

Heron acknowledges that the failure-of-others test requires showing a demand and that "others tried but failed to satisfy that demand." D.I. 180 at 52 (quoting *In re Cyclobenzaprine*, 676 F.3d 1063, 1082 (Fed. Cir. 2012)). Heron's argument is built on a flawed premise that because there was no commercial IV aprepitant emulsion product available before Cinvanti, that must mean "others tried but failed" to make an IV aprepitant formulation. Heron did not show that a skilled person tried and failed to develop such formulations. Heron primarily relies upon an inference that Merck must not have been able to develop an IV aprepitant formulation, because Merck commercially sold an IV fosaprepitant formulation. Heron offered no evidence to support that inference. Dr. Hale was not a formulator, and admitted that he was not testifying about any specific

IV aprepitant formulations that Merck tried. 971:22-25, 990:16-991:14 (Hale). Neither Dr. Hale nor Dr. Little testified about Merck's formulation work, much less any published work by anyone that showed formulation attempts that did not work. *In re Couvaras*, 70 F.4th 1374, 1381 (Fed. Cir. 2023) (finding investigation into alternative approaches "is not a failure" for patented approach). Even for chemical compound development, Merck synthesized both aprepitant and fosaprepitant at the same time (1993), JTX82.7, so there is no basis to infer that Merck tried formulating aprepitant and only later settled on fosaprepitant; it already had the injectable water-soluble fosaprepitant compound.

Heron further infers that because companies pursued other active compounds, that must mean they were unable to formulate aprepitant. But Heron showed no such evidence. A company has any number of reasons to make and use new compounds, having nothing to do with formulation. *See, e.g.*, 983:4-9 (Hale); 768:21-769:13 (Sullivan). Dr. Hale conceded that aprepitant itself was still under patent until around the priority date, 982:7-15, providing another non-formulation reason to work with other drugs until the priority date. Heron asserts that Fresenius Kabi made a fosaprepitant formulation, D.I. 180 at 20 n.9, but does not (and cannot) assert this was a reformulation, as opposed to a generic version of the approved Emend IV product.

The prior art also showed successful aprepitant formulations. CN845 and Zhou successfully made injectable formulations, and showed at least some stability information in the form of sterility testing and K_e optimization. Heron repeats its irrelevant assertion that these formulations did not result in commercial products. In *Novartis*, the court rejected the patentee's argument that "a feature known in the art but not actually available in the market…cannot be used to disprove [patentee's] attempts to establish a nexus…." *Novartis*, 853 F.3d at 1330. That Novartis brought the first commercially available solid oral dosage form of the drug for treatment

of the claimed indication was irrelevant because the prior art provided that very teaching. *Id*. at 1330-31. The same is true here: that Heron had the first aprepitant emulsion product to market is irrelevant because CN845 already disclosed aprepitant emulsions. Heron cites to *Knoll* to argue that failure to obtain FDA approval can be relevant. D.I. 180 at 54 (citing *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004)). But *Knoll* involved the scenario where others had ***tried and failed*** to obtain FDA approval. *Id*. There is no such evidence here.

Finally, Heron also relies on Hingorani's statement that "to the best of [its] inventor's knowledge no such soluble and stable formulation of aprepitant has been reported" to argue that CN845 and Zhou were failures. D.I. 180 at 54 (citing JTX21.2). But Hingorani never mentioned CN845, and Zhou post-dated Hingorani's application date, so Heron's argument is baseless. If anything, Hingorani expressly reported yet one more prior art formulation success story.

D. Heron's Unexpected Results Evidence Is Contrary To The Law And Facts.

Heron failed to show a POSA had any particular expectation regarding the stability of the products of CN845 ***before*** its claimed invention, or indeed anything based on the prior art. It did not show "unexpected" results. *Pfizer*, 480 F.3d at 1371.

1. Heron's Examples 4 and 5 Show Expected Increased Stability By Adding Emulsifier

Heron relies on its "duplications" of CN845 and Zhou. These cannot show the basis for unexpected results, because the stability results Heron obtained were not in the prior art. If anything, Examples 4 and 5 show that Heron did exactly what a POSA would have done—add more emulsifier to further stabilize the product. Indeed, if a POSA tested CN845 and found four days stability, then a POSA would have been able to routinely make adjustments by adding emulsifier to further increase stability to meet USP standards. *See Asyst*, 544 F.3d at 1315-16 (holding no unexpected results where the only difference between the claims and the prior art—

the use of a multiplexer—was "well understood at the time of the [asserted] patent application"). In short, "the theories presented during [prosecution] proved too weak when challenged in a judicial forum to rise to the level of unexpected results sufficient to rebut a strong case of obviousness." *Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1353 (Fed. Cir. 2015).

Heron's references to the named inventors' work (D.I. 180 at 6-8) also show that the inventors simply took the very "trial and error" steps a POSA would have taken in modifying CN845 to arrive at a stable formulation. 464:21-465:6 (Han); DTX283_9. Ordinarily, the inventor's path to the alleged invention is not relevant to the obviousness inquiry. *See Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000). However, courts may rely on testimony and evidence regarding scientific principles known by a POSA that are followed by and applied by the inventor in evaluating obviousness. *See UCB, Inc. v. Actavis Labs. UT, Inc.*, 65 F.4th 679, 695 (Fed. Cir. 2023) (finding no error where district court relied on testimony that a POSA would have, just like the patentee, increased the prior art amount of PVP to crystalize).

2. Increased Stability Is A Difference In Degree

Heron next attempts to portray the stability difference as a difference in kind versus degree, but its own argument proves the contrary. D.I. 180 at 55. Heron cites to Dr. Ottoboni's testimony that "if a formulation is not stable for one week 'it becomes almost impossible to commercialize.'" D.I. 180 at 55 (quoting 541:23-542:7). The difference between four and seven days, however, is still a difference in degree, even if seven days makes it more possible to commercialize the product. As Dr. Rabinow explained, these are differences in time, which are not changing the way the drug works but only how long it remains stable, which is a matter of degree. 293:3-294:6.

3. Heron's New 2-Minute Push Argument Fails

Heron raises a new attorney argument that the ability to administer the claimed composition as an IV push was unexpected. D.I. 180 at 55 (asserting without citation that claimed formulations

"also were safe for administration through IV push"). No expert testified that the 2-minute push had anything to do with the claimed formulation or that it was "unexpected." Nor could any expert have claimed some unexpected benefit over the prior art, since CN845 already disclosed formulations that could be administered as an "injection" (a push) or as an "infusion" (a longer administration). 1355:10-1356:3, 1358:8-22 (Little); DTX71.13. Moreover, because it relates to administration time, the difference is in degree and not kind; Heron did not show otherwise.

E. Heron Fails To Address Evidence Showing No Commercial Success.

Heron failed to establish a nexus between sales of Cinvanti and the Asserted Claims. "[I]f the commercial success is due to an unclaimed feature of the device" or "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1034 (Fed. Cir. 2016) (quoting *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006)). Heron does not even mention, much less address, Mr. Masztak's testimony and explanation that strategic pricing drove sales. Mr. Tate himself testified that, rather than seek a premium price based on any supposed advantages, Heron had to compete only on price because of other available alternative drugs. 1159:10-1160:5.

Heron has no legal support for its argument that "maintaining market share" is an indication of commercial success; as a result, it distorts the record regarding the proper market. Specifically, Heron notes that "[t]here is no dispute that Cinvanti's economic market is intravenous NK-1 receptor antagonists." D.I. 180 at 56 n.24. But Dr. Markman's unrebutted testimony was that doctors use oral antiemetics including oral NK-1 receptor antagonists, 576:24-577:20, 637:4-638:14, 640:22-641:9, 659:13-660:12; 692:14-694:11, and the NCCN Guidelines on which Heron and Dr. Roeland rely specifically provide that oral NK-1 receptor antagonists are a treatment regimen option, JTX142.14; *see also* 1194:20-1195:12 (Tate). Both medical experts agreed that there are benefits to, and a preference for, IV antiemetic formulations, 701:1-11 (Markman);

1017:12-1018:7 (Roeland), but the point remains that the two are considered alternatives in the same market, 694:7-11, 700:8-25 (Markman).

F. Heron Agrees ANDA Copying Allegations Are Not Relevant.

The parties agree that "evidence of copying required by the Hatch-Waxman Act is not considered probative in the ANDA context." D.I. 180 at 58. Heron implies that copying of claim elements not required by the Hatch-Waxman Act is relevant. Here, however, every element of the Asserted Claims is required in order for a product to be a Q1/Q2 ANDA product. 25:15-26:4 (Little). Any alleged copying is irrelevant. Heron uses its implication as a prelude to argue that Fresenius Kabi should have changed the Cinvanti formulation, ignored the ANDA pathway, and filed a 505(b)(2) application instead. Under that reasoning, however, every ANDA would be automatically a "copy" for not having pursued a 505(b)(2) alternative, which is not the law. *Adapt Pharma Ops. Ltd. v. Teva Pharm. USA*, 25 F.4th 1354, 1374 (Fed. Cir. 2022). That would also defeat the purpose of the Hatch-Waxman statutory and regulatory regime for ANDAs.

G. Heron No Longer Asserts Skepticism.

Heron does not mention skepticism as part of its secondary considerations discussion in its opening brief. Out of an abundance of caution, to address the passing reference of the word "skeptical" in its obviousness section (D.I. 180 at 44), there was no evidence of skepticism. Heron offered no prior art reference that identified any skepticism about making an intravenous formulation, and by the priority date, CN845 had already made one.

IV. Heron's Infringement Assertion Relies On, And Thus Concedes, Inherency

Heron never mentions inherency, so seems to have conceded it. In fact, Heron's infringement argument expressly relies on inherency. Heron points to its own microscopy testing, and then applies it to Fresenius Kabi's product, on the basis that the formulations are the same; Heron relies on no other variables or information. D.I. 180 at 16. *Sunovion* is inapposite here,

because Fresenius Kabi does not have any specification based on microscopy, and Dr. Little admitted the test Fresenius Kabi did was a "naked eye" test. 56:2-10 (Little); *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1278-79 (Fed. Cir. 2013).

Heron cites the *Bristol-Myers* decision to allege that the test for crystal content to determine "physical stability" is irrelevant. D.I. 180 at 16. *Bristol-Myers* is inapposite to this case. Unlike in *Bristol-Myers*, the Court's claim construction here, not Fresenius, requires a test of 4x-10x magnification. *See Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.*, 477 F. Supp. 3d 306, 343 (D. Del. 2020). Ultimately, if 4x-10x magnification really means 40x-100x, then Heron can only show that Fresenius Kabi's formulation meets the magnification requirement by relying on inherency. The same data, D.I. 180 at 14-16, shows that obvious prior art formulations with 14% egg yolk lecithin would also have inherently met the "physically stable" limitation. Otherwise, Heron has not proven infringement because it did not test Fresenius Kabi's ANDA product or otherwise show that it meets the microscopy requirement for claims 9 and 10 of the '794 patent.

Heron did not address the Asserted Claims separately, as the invalidity analysis does substantially overlap, with one important difference: the '229 patent does not require "physically stable" formulations and the '794 patent does. This is significant for inherency, because if the formulations claimed in claims 9 and 10 of the '229 patent would have been obvious to a POSA pursuing any aspect of USP physical stability, then those formulations inherently would have included all of the claimed physical stability properties as to claims 9 and 10 of the '794 patent.

V. The Asserted Claims Lack Written Description

A. The Specification Does Not Show Possession Of The Full Scope Of pH Range

Heron does not dispute that "stable formulations [were] all done in a very narrow pH range of something like 8.7 to 8.8." D.I. 180 at 59 (quoting 306:25-307:3 (Rabinow)). Heron relies on *Vanda*; there, the specifically claimed "12 mg/day" dose was not tested for poor-metabolizer

patients, but the specification disclosed other tests that "show[ed] a trend" towards the claimed dose and disclosed examples reducing the standard 24 mg/day dose "by a factor of 1.5 to 3.5." *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1136-37 (Fed. Cir. 2018). Based on the test results, the Court could not "say the district court clearly erred." *Id.* at 1337.

In this case, there is nothing to show that the named inventors possessed the claimed invention, particularly the 7.5-8.0 claimed portion of the pH range. Instead, examples where the pH was 8.74-8.92 were shown to be "physically stable"; whereas, Example 4 used pH 7.0, which Heron used as a representative formulation "which was adjusted to a pH of less than 8.0," and that Example showed crystals at four days. JTX1.15. Dr. Rabinow discussed the importance of pH, further supporting the need to have shown this full pH range. 163:20-164:20, 286:6-17. Heron's reliance on extrinsic evidence like Cinvanti and Fresenius Kabi internal reports is misplaced; written description is based on the "four corners of the specification" itself. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Heron did not distinguish between Asserted Claims, noting all "inventive examples" demonstrated "stability." D.I. 180 at 60.

B. For Claim 21, The Parties Agree That Efficacy Would Have Been Expected

As to claim 21, Heron validates Fresenius Kabi's evidence that a POSA would have reasonably expected to practice the claimed method with an IV aprepitant emulsion. D.I. 180 at 60 (arguing that any challenge to aprepitant's expected efficacy "goes against the state of the art"). Far from disputing reasonable expectation of success, Heron endorses it. *Id.* (citing 594:20-595:14, 596:4-11 (Markman) (testifying regarding JTX71.14)).

VI. Conclusion

For all the reasons set forth herein and in its Opening Brief (D.I. 179), Fresenius Kabi respectfully requests the Court to issue judgment in Fresenius Kabi's favor.

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